RESEARCH ARTICLE

Evaluation of *In vitro* Antacid Activity of Two *Evolvulus* Spp. and Formulation of a Novel Drug Delivery System Using the Crude Plant Powder

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ABSTRACT
The study investigates the pharmacognosy and *in vitro* antacid activity of *Evolvulus alsinoides* (L.) L. and *Evolvulus nummularius* (L.) L. plant species, that would be used in the formulation of a stable antacid dosage form. Pharmacognostic analyses, phytochemical screenings, and *in vitro* gastric acid-neutralising activity assay were performed on both of the species. Formulated *E. alsinoides* chewable granules were subjected to stability assessments under accelerated conditions. *E. alsinoides* and *E. nummularius* resulted in more fibres and more crystals in the respective powder samples. Aqueous and ethanolic extracts of both plants produced positive results for common phytochemicals (e.g., flavonoids, alkaloids, phenolics, etc.), but cardiac glycosides were absent in aqueous extracts. Antacid activities of *E. alsinoides* and *E. nummularius* were statistically significant ($p<0.001$) with the respective negative controls. The granules formulated using *E. alsinoides* plant powder were sufficiently stable in pH value (pH: 5.36±0.01), chemical composition, and acid-neutralising activity (0.16±0.00 H^+ mmol) throughout the study period. Detailed pharmacognostic characteristics revealed by this study can be used in the differentiation of *E. alsinoides* and *E. nummularius*. Both species possess significant antacid activity. Although the *in vitro* bioactivity of formulated granules remained constant under accelerated conditions, their stability performances have to be improved.

Keywords: Antacid, Chewable granules, *Convolvulaceae,* Pharmacognosy, Stability testing
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INTRODUCTION

A considerable proportion of the world population still uses traditional medicine to fulfil their health requirement and most of these traditional systems involve the use of crude or purified plant extracts or isolated active components.[1] Plants belonging to the genus *Evolvulus* from the family *Convolvulaceae* are usually utilised to treat neurological disorders and are known collectively as 'Vishnukranthi' despite being comprised of several distinct species. These plants grow mainly in tropical and sub-tropical regions. *Evolvulus alsinoides* (L.) L. bears blue colour flowers, which can be used as the key morphological feature to distinguish the plant from *Evolvulus nummularius* (L.) L., a related species which bears white flowers.[2] The whole mature plant of *E. alsinoides* is used to treat dementia, dysentery, syphilis and many other diseases whereas *E. nummularius* is also acknowledged with similar types of ethnomedicinal uses such as in convulsions, spasms and gastric disorders.[3,4] It had been proven in previous studies that dry powder of *E. alsinoides* whole plant has demonstrated a dose-dependent gastroprotection in rats by several biological mechanisms including the reduction of gastric acid secretion.[5] A medicinal oral paste which had been formulated with *E. alsinoides* powder has also produced significant gastroprotection in Wistar rats in another study.[6] Pharmacognostic studies are a powerful tool to provide a thorough description of the plant material, which can be then used in the standardisation and pre-formulation studies.[7] Many pharmacognostic analyses have been carried out on Indian varieties of *E. alsinoides* and *E. nummularius*. However, studies on Sri Lankan varieties are found to be either inadequate or unavailable.[8,9] Since these plants have drawn attention in gastroenterology recently, the present study was directed to formulate a stable oral dosage form using *Evolvulus* spp. to treat peptic ulcer disease. Also, it is noteworthy that the bioassay methods employed in this study are well-established but underutilised *in vitro* methods. Chewable dosage forms are novel drug delivery approaches and got wide attention due to their higher patient compliance and ease of

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Table 1: Formula of the *Evolvulus alsinoides* chewable granules

Ingredients	Percentage (w/w %)
Dry powder of *E. alsinoides*	30.0
Mannitol BP	30.0
Maize starch BP	30.0
Pregelatinised starch (10% w/v)	As needed
Chocolate flavour	As needed
Colouring agent	As needed

Table 2: Physicochemical characteristics of *Evolvulus alsinoides* and *Evolvulus nummularius*.

Physicochemical properties	Plant sample (values in w/w %)	
	E. alsinoides	*E. nummularius*
Moisture content	9.12 ± 0.00	9.60 ± 0.00
Total ash value	8.49 ± 0.03	9.36 ± 0.03
Water-soluble extractable matter	15.43 ± 0.05	17.28 ± 0.29

Values are given as mean ± standard error (n=5)

manufacture.[10] The changes in the stability parameters of any dosage form will lead to the potency loss of the drug, in addition to pharmaceutical toxicity.[11] Hence in this study, a cost-effective but standard and comprehensive accelerated stability study was done on *E. alsinoides* powder incorporated chewable granules, as a part of its pre-formulation investigations.

MATERIALS AND METHODS

Collection and plant authentication

Flower-bearing, healthy mature plants of *E. alsinoides* and *E. nummularius* were collected from Sri Lanka in February 2019. Both plant samples were air-dried and then authenticated by the National Herbarium, National Botanical Gardens, Peradeniya, Sri Lanka under herbarium number 6/01/H/03-01a for *E. nummularius* (L.) L and 6/01/H/03-01b for *E. alsinoides* (L.) L.

Pharmacognostic and phytochemical evaluation

Both plants were subjected to microscopic evaluation of fresh and powdered samples,[12] and physicochemical characterisation[7] as described in the literature. Phytochemical screening was carried out for the ethanolic and aqueous crude extracts of *E. alsinoides* and *E. nummularius* whole plants. Dried 12.0 g samples of each plant powder were hot refluxed with 250.0 ml of either distilled water or ethanol for 3 hours separately. Methods described in the literature were employed in the screening of key phytoconstituents in the extracts i.e. alkaloids, phenolics, tannins, flavonoids, cardiac glycosides, and terpenoids (monoterpenes and sesquiterpenes).[13]

Assessment of *in vitro* antacid activity of *Evolvulus* species

Air-dried healthy *E. alsinoides* and *E. nummularius* (16.0 g each) plants were refluxed for 4 hours with 400.0 ml of distilled water separately. The concentrations of the extracts were subsequently determined as 53.33 mg/ml. The method

Table 4: Results of the microbiological stability parameters in accelerated stability study of Vishnukranthi chewable granules on day 0 and 90.

Test day	Number of CFU in TVBC assay	Number of CFU in TVFC assay
Day 0	80.33 ± 5.78	3.00 ± 1.53
Day 90	204.70 ± 7.69[a]	25.33 ± 6.89

CFU: colony-forming units; TVBC: total viable bacterial count; TVFC: total viable fungal count, Values are given as mean ± standard error (n=3), Significant [a]p<0.05 compared to the result of respective parameter on day 0, paired t-test

Figure 1: 'Vishnukranthi' chewable granules.

Table 3: Results of the physical stability parameters in accelerated stability study of Vishnukranthi chewable granules on day 0, 30, and 90.

Test day	Percentages of fine particles (w/w %)	Moisture content (w/w %)	pH value
Day 0	0.56 ± 0.10	9.33 ± 0.18	5.36 ± 0.01
Day 30	1.28 ± 0.10[a]	8.67 ± 0.13[a]	5.36 ± 0.00
Day 90	1.47 ± 0.01[a]	7.73 ± 0.13[ab]	5.35 ± 0.00

Values are given as mean ± standard error (n=3), Significant [a]p<0.05 compared to the result of the respective parameter on day 0, [b]p<0.05 compared to the result of the respective parameter on day 30, ANOVA

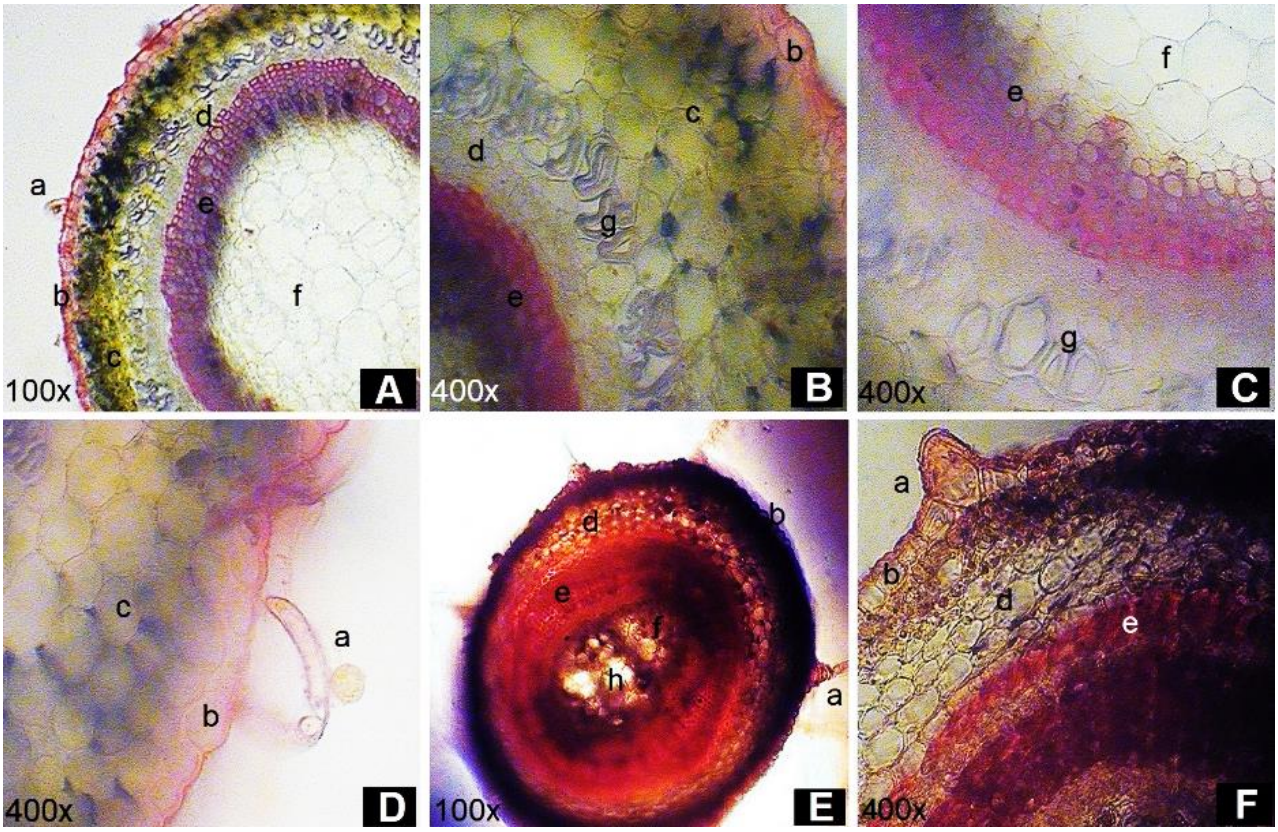

Figure 2: Microscopic views of the cross-section of (A-D) *Evolvulus alsinoides* stem, (E-F) *Evolvulus nummularius* stem; a: trichome, b: epidermis, c: hypodermis, d: cortex, e: vascular area, f: pith, g: endodermis cells, h: starch granules

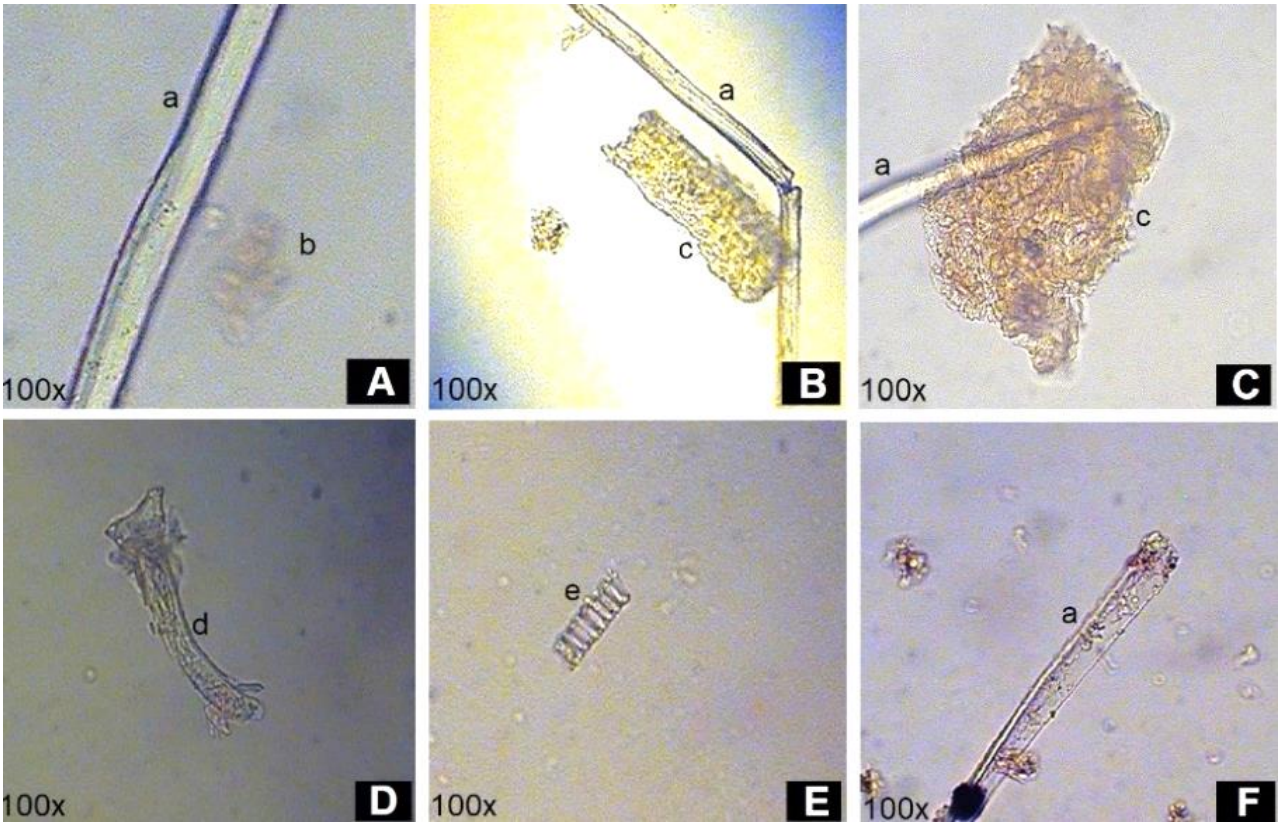

Figure 3: Powder microscopy of (A-C) *Evolvulus alsinoides*, (D-F) *Evolvulus nummularius*; a: sclereidal fibre, b: starch granules, c: xylem vessel fragment, d: trichome, e: crystals

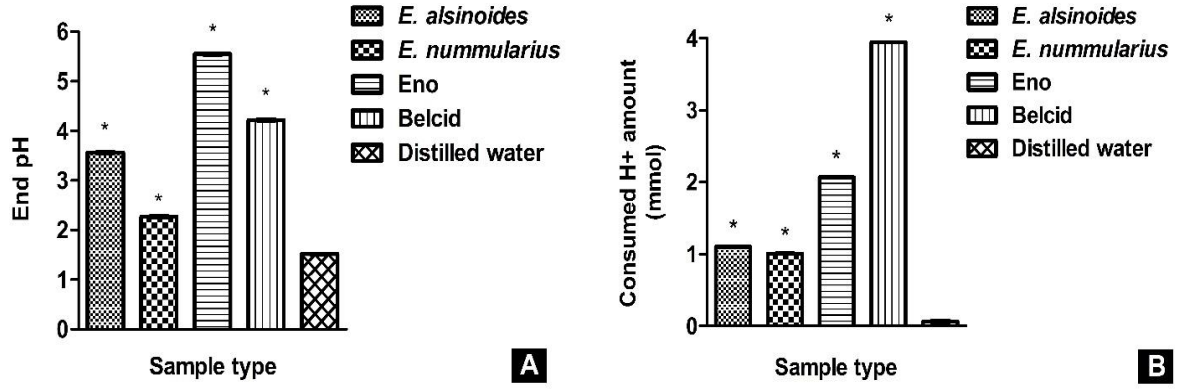

Figure 4: Aqueous extracts of *Evolvulus alsinoides* and *Evolvulus nummularius*, Eno®, and Belcid® in (A) neutralising effect assay, (B) neutralising capacity assay; Values are given as mean ± standard error (n=3); Significant *p<0.001 compared to respective controls, ANOVA

described in the literature was used to prepare pH 1.2 artificial gastric acid.[14] Two commercial antacid preparations, i.e., Eno® (substance A) and Belcid® (substance B) were used as the positive controls at their clinically recommended doses. Distilled water was employed as the negative control of the experiment. The aqueous plant extracts of *E. alsinoides* and *E. nummularius* were subjected to *in vitro* neutralising effect assay and neutralising capacity assay using artificial gastric acid.[15]

Neutralising effect on artificial gastric acid

Freshly prepared artificial gastric acid (10.0 ml) was placed in a beaker and aqueous extracts of *E. alsinoides, E. nummularius*, positive or negative controls in 9.0 ml quantities were added separately into the acid. After shaking the beaker for continuous 5 minutes, the final pH was determined as the parameter of the neutralising effect.

Neutralising capacity by Fordtran's titration method

Freshly prepared artificial gastric acid was filled into a burette and 9.0 ml of test samples were titrated with it in a beaker at 37 ^{0}C. A magnetic stirrer was used to agitate the sample continuously at 30 rounds per minute speed. Titration was done as per Fordtran's procedure and then discontinued when the pH of the test solution became 3.00. The total amount of H^+ ions consumed by each sample was determined finally.

Formulation of 'Vishnukranthi' chewable granules

In vitro assays conducted in the present study revealed comparatively higher antacid activity ($p<0.05$) in *E. alsinoides* aqueous extract than the *E. nummularius* aqueous extract. Therefore, only *E. alsinoides* was used in the formulation of the chewable granular dosage form (Figure 1). The master formula of the ingredients of *E. alsinoides* chewable granules is given in Table 1. All of the excipients used were of pharmaceutical grade. *E. alsinoides* whole plant was air-dried under shade for fourteen days and grounded to get a powder (Waring laboratory, 8010ES, USA). The powder was then passed through a 0.15 mm sieve and fine powder was collected under aseptic conditions. This dry powder was then mixed with pregelatinized starch (10% w/v) portions and other excipients, while thorough kneading. The stiff dough was

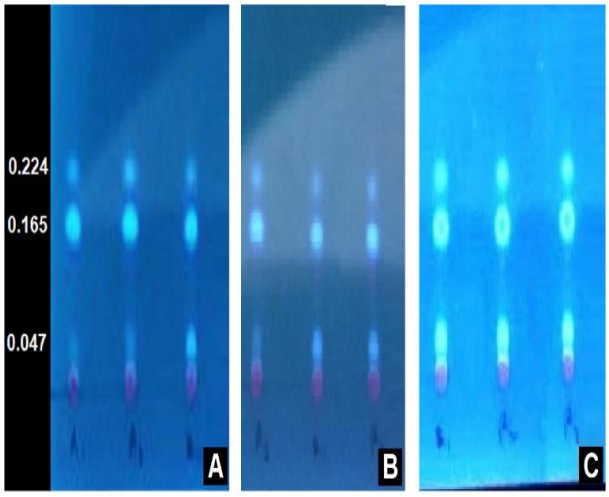

Figure 5: Thin-layer chromatograms of chewable granules on (A) day 0, (B) day 30, and (C) day 90 recorded under the 366 nm wavelength (n=3)

then passed through a 2.0 mm sieve mesh to form wet granules. Finally, the granules were oven-dried at 50 ^{0}C for 2 hours with occasional turnings to expose wet areas.

Accelerated stability testing of 'Vishnukranthi' chewable granules

Stability was studied for a period of 3 months under the accelerated conditions that are stipulated by the World Health Organization, i.e., 40±2 ^{0}C storage temperature and 75±5% relative humidity. All the accelerated stability data were documented on the day of manufacturing (day 0) and were repeated after 1 (day 30) and 3 (day 90) months.[16]

Physical stability testing

Physical stability parameters (particle size distribution, moisture content, and pH) were evaluated according to the methods prescribed by the British Pharmacopoeia (2019). For sieve analysis, a series of sieves were occupied and the weights of particles left in each sieve were plotted against the mesh size. Moisture content of the granules was determined by drying 5.0 g of granules sample at 105 ^{0}C for a constant weight. For the pH testing, a 10.0 g aliquot of granules was dissolved well in distilled water and the pH value was tested on each test day.[17]

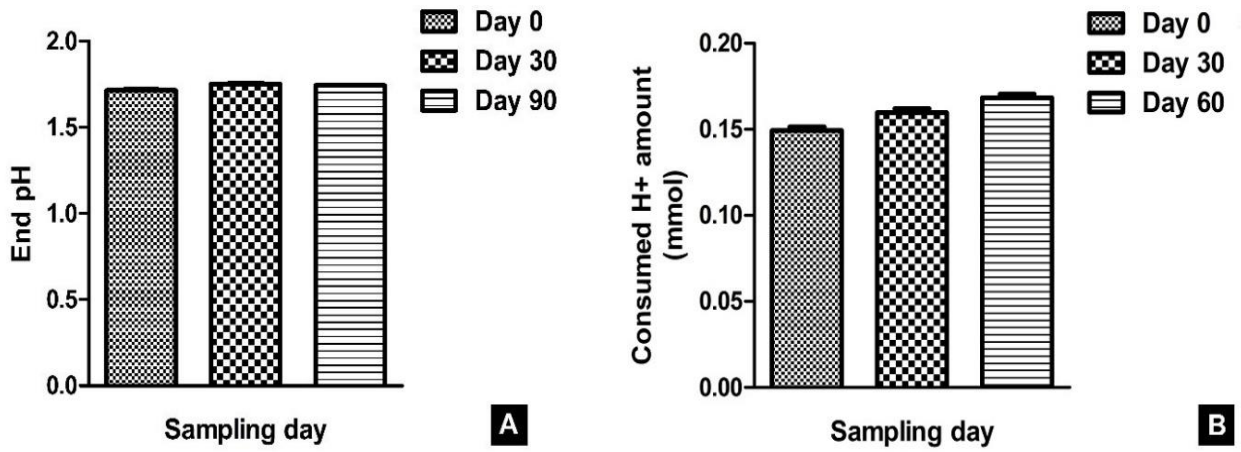

Figure 6: *In vitro* acid neutralising activity of the chewable granules on day 0, 30, and 90 in (A) neutralising effect assay, (B) neutralising capacity assay; Values are given as mean ± standard error (n=3); Significant *p<0.05 compared to the result of respective parameter on day 0, ANOVA

Chemical stability testing

The chemical stability was assessed by comparing the thin-layer chromatography profiles of the formulation on each test day. A 15.0 g aliquot of granules was extracted with a 25.0 ml portion of methanol in an electronic shaker for 2 hours. The filtered sample was then developed on precoated, normal-phase silica plates (Sigma Aldrich, Germany) by using the following solvent system - toluene: ethyl acetate: formic acid at 7.5:1.5:1.1 (v/v/v).[18]

Microbial stability testing

The pour-plate method and conditions prescribed by the British Pharmacopoeia (2019) were employed in the determination of the total viable aerobic bacterial count (TVBC) and total viable fungal count (TVFC) of the dosage form on each test day. A diluted series of granules (1:10, 1:100, and 1:1000 w/v) were prepared suitably using sterile saline (the negative control). The average number of bacterial or fungal colony-forming units (CFU) in each plate was determined after the incubation period of 5 days.[17]

***In vitro* antacid activity of the granules under accelerated conditions**

A 15.0 g quantity of chewable granules was dissolved in 90.00 ml of distilled water to obtain a solution which contained equal concentrations of *E. alsinoides* on each test day. This solution was gravity-filtered to remove the insoluble matter included in the formulation. Then 9.00 ml portions of the filtrate were subjected to *in vitro* neutralising effect and neutralising capacity assays similarly according to the methods mentioned previously.

Statistical analysis

All the experimental data were analysed statistically by SPSS 25 software at significant levels of 0.001, 0.01, or 0.05 where necessary. Each test was compared with suitable negative controls and given as mean ± standard error of mean unless otherwise specified in each circumstance.

RESULTS

Pharmacognostic and phytochemical evaluation

Microscopic evaluation of samples

The microscopic views of *E. alsinoides* and *E. nummularius* stem cross sections are presented in Figure 2. Both plants consisted of dicotyledon-type vascular bundles which were arranged along the periphery of the stem. Both plants contained single-layer epithelia which were abundant with non-glandular, uniseriate or unicellular trichomes. The hypodermal cell layers of both plants were found to contain a large number of chloroplasts. Additionally, a prominent endodermis was observed in *E. alsinoides* stem which contained cells with thick cell walls. The pith of *E. alsinoides* was prominent and contained polygonal to circular parenchymal cells. *E. nummularius* had an apparently smaller pith with starch granules located in the centre. The dry powder of *E. alsinoides* was brownish-green under visible light and was slightly bitter when evaluated organoleptically. The same observations were made with the dry powder of *E. nummularius* whereas both coarse powders possessed characteristic herbal odours. According to the powder microscopic features of both plants presented in Figure 3, *E. alsinoides* consisted of sclereidal fibres, starch granules, cork cells, and fragments of xylem vessels in the sample. *E. nummularius* also carried fibres and xylem fragments but remarkably contained a large number of differently shaped free crystals in the observed plant tissue samples.

Physicochemical assessment of samples

Table 2 presents the physicochemical properties of the study plants. Both *E. alsinoides* and *E. nummularius* contained almost similar moisture content. However, the determination of total ash values and water-soluble extractable matter contents showed that those parameters are quantitatively higher in *E. nummularius* compared to *E. alsinoides*.

Preliminary phytochemical screening

All the ethanolic and aqueous extracts of *E. alsinoides* and *E. nummularius* were positive for tannins, saponins, flavonoids, and phenolic compounds. Aqueous extracts of both plants were devoid of terpenoids (monoterpenes and sesquiterpenes) however, considering the ethanolic extracts, both plants were positive for terpenoid

compounds. Interestingly cardiac glycosides were only present in *E. alsinoides* ethanolic extract whereas the same sample was negative to alkaloid assays, deviating from the other tested extracts.

***In vitro* antacid activity of *Evolvulus* species**

The neutralising effect of *E. alsinoides* (pH: 3.56 ± 0.00) and *E. nummularius* aqueous extracts (pH: 2.27 ± 0.00), substance A (pH: 5.55 ± 0.0), and substance B (pH: 4.217 ± 0.01) were significant with the negative control ($p<0.001$) as shown in Figure 4A. Considering Figure 4B which illustrates the outcomes of the neutralising capacity assay, mean values of consumed H^+ amount by all the test substances were also found to be statistically significant with the negative control ($p<0.001$). Both assays showed that *E. alsinoides* aqueous extract has a statistically higher antacid activity compared to *E. nummularius* ($p<0.001$).

Stability of 'Vishnukranthi' chewable granules

Physical stability

Table 3 indicates the physical stability data of the chewable granular dosage form. The percentages of fine particles showed that there were significant differences in the day 30 ($p<0.05$) and day 90 ($p<0.05$) accelerated samples compared to the sample at day 0. Percentages of weight loss on drying (LOD) also demonstrated significant differences ($p<0.05$) between the day 0 sample with accelerated samples. The LOD was found to be reducing continuously with time, since smaller LOD values were observed with consecutive accelerated samples, compared to day 0. However, the granular dosage form did not exert significant changes in its pH value, as the pH of the sample on day 0 was comparable with day 30 ($p>0.05$) and day 90 ($p>0.05$) accelerated samples. Moreover, the pH values of the accelerated samples on day 30 and day 90 were also found to be comparable to each other ($p>0.05$).

Chemical stability

Thin-layer chromatograms of the oral granules were recorded under the 366 nm ultraviolet wavelength on day 0, day 30, and day 90 and are shown in Figure 5. Three considerable spots were observed in each sample with Rf values of 0.047, 0.165, and 0.224. The Rf values of the spots were noticed to be consistent during the study period.

Microbial stability

Since the number of CFU per plate in the TVBC assay was >300 in 1:10 and 1:100 dilutions, they were eliminated from the consideration. The 1:1000 dilution in TVBC exerted a significantly higher count ($p<0.05$) on the day 90 accelerated sample compared to the day 0 sample. Since the number of CFU per plate in the TVFC assay was <200 in 1:10 dilution, the other two dilutions were eliminated from the consideration. A significantly higher count ($p<0.05$) was observed on the day 90 accelerated sample compared to the day 0 sample. Results of the microbial stability assays are given in Table 4.

***In vitro* antacid activity of the chewable granules**

According to Figure 6, the acid-neutralising effect and neutralising capacity of chewable granules did not possess significant changes ($p>0.05$) on day 30 (1.75 ± 0.01 pH and 0.16 ± 0.00 H+ mmol) and day 90 (1.74 ± 0.01 pH and 0.17 ± 0.00 H+ mmol) accelerated samples, compared to the day 0 sample (1.71 ± 0.01 pH and 0.15 ± 0.00 H+ mmol) of respective assay. Also, the activity of day 30 and day 90 samples were found to be comparable ($p>0.05$) to each other in both *in vitro* assays. Hence, the antacid activity of the chewable granular dosage form appeared to be constant for the accelerated stability study period.

DISCUSSION

Herbal medicines are utilised in many of the traditional medical systems and they act as a good source of potent and cost-effective treatment alternatives in health care management.[7] Both *Evolvulus alsinoides* and *E. nummularius* are known as 'Vishnukranthi' in ethnomedicine, and thus adulteration is a considerable issue in their authentication.[18] In previous botanical studies, it has been well demonstrated that plants grown in wet climates are more prone to contain higher moisture levels compared to plants inhabited in dry zones.[19] However, the moisture content of *E. nummularius* was found to be almost similar to *E. alsinoides*, despite the different climate zones (wet and dry respectively) they chiefly inhabited in the country. Thus, both plant materials show no advantage over one another considering the stability against chemical and microbiological degradation, though moisture plays a crucial role in such instances.[20] In the present study, the Sri Lankan variety of both *E. alsinoides* and *E. nummularius* were reported to contain flavonoids, phenolics, terpenoids, and alkaloids in aqueous and/or ethanolic extracts. Indian and African varieties of *E.* alsinoides had resulted in dissimilar phytochemical profiles in some other studies and hence emphasises the need for distinct studies on varieties of the same plant species.[21,22] Since many phytoconstituents have been proven to be responsible for the antacid activity exerted by different plant materials, gastroprotection produced by study plants is also predictable.[23] A wide array of phytochemical constituents had been isolated in the ethanolic and other extracts of the Indian *E. alsinoides* variety, such as evolvoside A-E, caffeic acid, coumarin derivatives, and different fatty acids.[24] The gastric acid neutralisation demonstrated by these diverse phytochemicals may vary depending on the electron-donating ability of different functional groups. In addition, nitrogen-containing metabolites such as 3-methyl-2,4-imidazolidinedione, 5-(furan-2-yl)-1,3,4-oxadiazol-2-amine derivatives, cytidine, and piperine which had also been isolated from the Indian *E. alsinoides* may exert acid neutralisation through their nitrogen atoms in free or substituted amino groups.[25] The present study investigates the *in vitro* neutralising activity of *E. nummularius* in addition to *E. alsinoides,* which would be the first-ever record of such activity in the plant. It was shown statistically that the acid neutralizing activity produced by *E. alsinoides* was significantly higher ($p<0.001$) compared to *E. nummularius* in both acid neutralising effect and acid neutralising capacity assays. Furthermore, previous *in vivo* studies have also disclosed the appreciable anti-gastric ulcer activity in the crude plant powder of *E. alsinoides*.[5] Hence, the study on oral dosage form formulation was continued with the plant *E. alsinoides.* Solid pharmaceutical formulations exhibit greater chemical and microbiological stability compared to liquid formulations due to their lower

moisture levels.[26] According to the inter-species dose interpolation of results from the previous animal studies, the safe human single dose of *E. alsinoides* powder was estimated to be 15.00 g in a 70.0 kg body weight.[27] Oral granules offer a convenient method for administering a such considerable amount of solid medication in a single dosage.[26] The oral granules were formulated in the chewable form, by incorporating mannitol as a sweetening agent to increase consumer compliance and also to mask the slight bitterness. Mannitol may also act as the diluent of the formulation along with maize starch which was the binding agent in the wet-granulation process. The sieve analysis of the stability study revealed that more granules have migrated towards the finer particle range (0.125 mm - 0.200 mm) during the accelerated period, hence the granules have become more susceptible to being broken down during handling and storage.[28] Although the moisture content of the granules has been reducing with time, it has not considerably contributed to the protection against bacterial bioburden of the dosage form, given that TVBC was significantly higher ($p<0.05$) at the end of the stability testing period compared to the initial manufacturing day. The pH considerably affects the stability of different phytochemical constituents in the dosage form such as phenolics, and has a significant impact on the consistent antacid bioactivity throughout the shelf life.[29] Agreeing that the pH of the dosage form has not been significantly changed during the stability period, which in turn resulted in comparable antacid activity on day 30 ($p>0.05$) and day 90 ($p>0.05$) with compared to the day 0 sample. Also, TLC fingerprints have not changed drastically, the study suggests that the main chemical species detectable by TLC at 366 nm remained consistent during the stability period.

Previous studies have demonstrated the significant gastroprotection produced by *E. alsinoides* as a crude powder as well as in oral paste form.[5,6] Oral paste is a common type of dosage form used in traditional medical systems but is found to be less user-compliant due to unacceptable organoleptic properties.[30] Therefore, the chewable granular form may be a good alternative to utilise the plant in a pharmaceutically acceptable drug delivery approach. Furthermore, an activity-guided fractionation process established on simple separation techniques is suggested to increase the potency and reduce the bulkiness of the tested herbal dosage form. Furthermore, real-time stability tests with more elaborated pharmacopeial parameters and detailed pre-clinical investigations will be needed for the further development of the dosage form.

CONCLUSION

Detailed pharmacognostic characteristics of *E. alsinoides* and *E. nummularius* can be used in the differentiation, though both plants share some similar physicochemical and phytochemical features. Both *Evolvulus* spp. hold statistically significant *in vitro* neutralising activities when compared to the control and hence can be used efficiently in formulating a chewable, granular dosage form. The formulated dosage form has to be pharmaceutically improved in terms of its physical and microbiological stability parameters but its acid neutralising bioactivity remains constant even under accelerated stability conditions during the test period.

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